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Increased Pelvic Vein Thrombi in Cryptogenic Stroke

Results of the Paradoxical Emboli From Large Veins in Ischemic Stroke (PELVIS) Study

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Background and Purpose—Cryptogenic stroke is associated with an increased prevalence of patent foramen ovale. The Paradoxical Emboli From Large Veins in Ischemic Stroke (PELVIS) study hypothesized that patients with cryptogenic stroke have an increased prevalence of pelvic deep venous thrombosis (DVT).

Methods—At 5 sites, patients 18 to 60 years of age received an MRI venogram (MRV) of the pelvis within 72 hours of new symptom onset. Clinical data were then determined. Radiologists blinded to clinical data later read the scans.

Results—The 95 patients who met entry criteria were scanned. Their mean \pm SD age was 46 \pm 10 years, and time from stroke onset to pelvic MRV scan was 49 \pm 16 hours. Compared with those with stroke of determined origin (n=49), patients with cryptogenic stroke (n=46) were significantly younger, had a higher prevalence of patent foramen ovale (61% versus 19%), and had less atherosclerosis risk factors. Cryptogenic patients had more MRV scans with a high probability for pelvic DVT (20%) than patients with stroke of determined origin (4%, $P<0.03$), with most having an appearance of a chronic DVT.

Conclusions—In this study of young stroke patients evaluated early after stroke, patients with cryptogenic stroke showed differences in several clinical features compared with patients with stroke of determined origin, including increased prevalence of pelvic DVT. The results require confirmation but suggest that paradoxical embolus from the pelvic veins may be the cause of stroke in a subset of patients classified as having cryptogenic stroke. (*Stroke*. 2004;35:46-50.)

Key Words: deep vein thrombosis ■ embolism, paradoxical ■ etiology ■ pathophysiology

No cause can be found in 26%¹ to 40%² of strokes and in 64% of stroke patients <55 years of age.³ Numerous studies have found that such cryptogenic stroke patients have an increased prevalence of patent foramen ovale (PFO) compared with patients with stroke of determined origin or normal control subjects, and a meta-analysis found this increase to be most significant in younger patients.⁴ A PFO is an interatrial communication that might allow thromboemboli to pass from the right to the left side of the heart. Patients with PFO-related stroke have an increased prevalence of inherited thrombophilic disorders.⁵ In patients with cryptogenic stroke, features of brain imaging are often suggestive of embolus.^{2,6} These facts together suggest that passage of venous thrombus to the cerebral arterial circulation might be the mechanism of stroke in some patients whose infarct is currently classified as cryptogenic, particularly younger patients. However, this formulation has been criticized because a venous source of thrombus has uncommonly been found in patients with stroke and PFO.⁷

Several findings suggest that pelvic veins may be an important source of thromboemboli in cryptogenic stroke. Autopsy studies have documented isolated pelvic vein or inferior vena cava thrombus in 16% of patients with pulmonary emboli (PE)⁸ and 22% of patients with paradoxical emboli in whom a source could be found.^{9,10} Clinical studies have identified pelvic deep venous thrombosis (DVT) in several populations,¹¹⁻¹⁴ including cryptogenic PE,^{15,16} suggesting that thrombi can form in pelvic veins and embolize. More recently, pelvic DVT has also been described in series of patients with cryptogenic stroke and PFO.¹⁷⁻²⁰

Prior studies suggest that pelvic veins may be an important source of thromboemboli and that the prevalence of PFO is particularly increased in younger patients with cryptogenic stroke. Limited information is available about pelvic DVT in young stroke patients, cryptogenic or otherwise. The Paradoxical Emboli From Large Veins in Ischemic Stroke (PELVIS) study was designed to test the hypothesis that, in young patients with

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TABLE 1. Characteristics of Study Population

	Cause of Stroke		<i>P</i> *
	Determined (n=49)	Cryptogenic (n=46)	
Age (SD), y	49 (7)	42 (11)	0.0002
Male, %	55	50	0.70
Prior history of			
Stroke, %	24	4	0.008
Hypertension, %	73	26	<0.0001
Diabetes mellitus, %	22	13	0.3
Hyperlipidemia, %	26	11	0.11
Coronary artery disease, %	18	4	0.052
Smoking, pack-year	17 (24)	7 (13)	0.02
Miscarriage,† %	10	22	0.4
Recent travel,‡ %	11	24	0.11
New antibiotic prescription,§ %	6	9	0.7
On exogenous estrogen, %	27	22	0.7
Current diagnosis of malignancy, %	0	2	0.48
History of DVT or PE, %	8	4	0.68

Values that are not a percent are mean.

*Based on 2-tailed *t* test or χ^2 test. No missing values.

†Among women only, who represented 22 patients with stroke of determined cause and 23 cryptogenic stroke patients.

‡A 3-hour car or plane trip in prior 2 weeks.

§Initiated in prior 2 weeks.

stroke, the prevalence of pelvic DVT is increased when stroke is cryptogenic compared with when stroke is of determined origin.

Patients and Methods

Entry Criteria

Eligible patients were 18 to 60 years of age, had ischemic stroke <72 hours in duration, and experienced deficits for >3 hours. The upper age limit was selected because review of the literature suggested that the association between PFO and cryptogenic stroke, a relationship relevant to investigation of pelvic DVT, is weaker beyond this cutoff; this value is similar to the upper age suggested in a recent meta-analysis.⁴ Exclusion criteria were inability to undergo an MRI scan, pregnancy, and stroke occurrence during hospitalization. An MRI venogram (MRV) was performed within 72 hours of stroke onset because studies suggest that formation of fresh DVT after stroke is uncommon when the interval is <3 days after stroke.^{21,22} Subsequently, a stroke neurologist ordered testing according to local practice standards to identify cause of stroke and classify²³ stroke subtype. Clinical data were collected prospectively. Each site attempted to enroll consecutive patients meeting entry criteria. Informed consent was obtained in all cases in accordance with local institutional review board requirements.

Clinical Assessments

Of 109 patients enrolled, 10 were determined not to have had a stroke, and 4 others could not be scanned, leaving 95 patients (Table 1) for these analyses. Four of these 95 patients were enrolled <72 hours after stroke but for technical reasons could not be scanned until 0 to 6 hours beyond the 72-hour cutoff. These 4 patients are included in current analyses because excluding them did not change significant findings. In 52% of patients (49 of 95), a cause of stroke was identified, whereas 48% (46 of 95) were classified as cryptogenic. Enrollment began September 1999 with 2 centers; 3 others were added mid-2000. Enrollment concluded February 2002.

MRV Acquisition

MRVs were acquired with a GE 1.5-T system and a phased-array torso coil to provide insights into venous structure and flow. Scanning consisted of 2-dimensional axial time-of-flight (TOF) and phase-contrast (PC) pulse sequences. The field of view extended 24 cm inferiorly from the infrarenal inferior vena cava to the common femoral vein just inferior to the inguinal ligament. In-plane resolution was 1.5×2.5 mm. For TOF images, a spoiled gradient-echo pulse sequence was used. Slices were 3 mm with 2-mm skip; repetition time was 47; and echo time was 3.5 ms. For PC images, slices were 5 mm thick without skip; slices were registered to TOF slices; repetition time was 45 ms; and echo time was 7.5 ms. PC images used a superior saturation band and velocity encoding value of 20 cm/s. Both pulse sequences used a 60° flip angle and 1 signal average. No contrast injection was used. MRV signal is affected by plane, caliber, and flow velocity of veins. MRV in the present study provided consistent data from external iliac veins, common iliac veins, and a portion of the inferior vena cava; a very short segment of the common femoral vein was also studied per the field of view. Internal iliac veins were seen to a lesser degree, and paraprostatic/parauterine veins could not be consistently evaluated.

MRV Interpretation

Pelvic MRV images were reviewed by 2 radiologists (J.H.M., L.A.K.) specializing in abdominal-pelvic imaging who were blinded to all clinical data. Each radiologist was randomly assigned half of the scans not acquired in his own institution. Before study enrollment, the radiologists devised criteria for acute and chronic pelvic DVT and then refined these criteria after reviewing pelvic MRV scans from a separate study.²⁰ Final criteria were similar to prior definitions for acute¹¹ and chronic²⁴ DVT.

Scans were judged as being high probability for pelvic DVT when there were at least 3 contiguous slices with a venous defect that was matched on TOF and PC images. A scan with intermediate probability for pelvic DVT had matched defects on only 2 contiguous slices. High-probability MRV scans were further classified as acute if the venous defect was a mural-based filling defect or as chronic if the vessel was narrowed without compression, often accompanied by circumferential thickening and/or collateral vessels. After final study interpretation of all scans, MRV scans with a high probability for DVT, along with 34 negative scans, were overread to assess interrater reliability.

Statistical Analysis

Continuous variables were compared with a *t* test; categorical variables, with Fisher's exact test or χ^2 test. All analyses were 2 tailed.

Results

Clinical assessments identified cause of stroke in 49 patients, representing 52% of total study population. Of these 49, 33% were due to a large-vessel event; 39%, a small-vessel event; 22%, a cardioembolic event; and 6%, another defined cause. In 1 patient, 2 possible causes for stroke were identified. No cause of stroke could be found in 46 patients (48% of the study population), the cryptogenic stroke group.

Patients with cryptogenic stroke were clinically distinct compared with patients with stroke of determined origin; they were 7 years younger and had significantly lower atherosclerosis risk factor prevalence. Several venous thrombosis risk factors such as recent travel or miscarriage showed a trend toward higher frequency in patients with cryptogenic stroke (Table 1).

Echocardiography was performed in 92% of patients (Table 2), including 44 of 46 patients (96%) with cryptogenic stroke. In 2 patients, interatrial shunt was diagnosed by transcranial Doppler. The prevalence of any interatrial shunt

TABLE 2. Clinical Assessments

	Cause of Stroke		<i>P</i> *
	Determined (n=49)	Cryptogenic (n=46)	
NIH Stroke Scale score at study entry	4	4	0.80
Weight (SD), lb	192 (42)	173 (44)	0.03
First serum BUN/Cr	16 (6)	15 (6)	0.20
First serum glucose, mg/dL	134 (50)	120 (46)	0.15
Stroke diameter, mm	35 (32)	31 (27)	0.50
Treated with IV tPA, %	20	17	0.80
Echocardiogram, %			
Done	86	96	0.16
Transthoracic	51	33	
Transesophageal	24	50	
Transthoracic+esophageal	10	13	
Atrial septal aneurysm present	0	9	0.11
PFO present	19	59	0.0002
ASD present	0	2	1.0
Leg venous duplex, %			
Done	20	52	0.002
Leg vein DVT present	2	0	0.30
Any of 6 hypercoagulation tests abnormal, %	16	27	0.39

NIH indicates National Institutes of Health; BUN, blood urea nitrogen; and ASD, atrial septal defect. Values that are not percent are mean, except NIH Stroke Scale score (median).

*Based on 2-tailed *t* test or χ^2 test. No missing values.

(PFO or atrial septal defect) across the study was 39%, with the rate in cryptogenic stroke patients (61%) being >3 times higher than in patients with stroke of determined origin. Hypercoagulation testing was performed inconsistently across patients, with 23% of patients receiving 0 of the 6 tests recorded by the study (anticardiolipin antibody IgG and IgM, activated protein C resistance, and levels of protein C, protein S, and antithrombin III). Leg vein duplex, ordered per clinical judgment, identified 1 leg DVT.

TABLE 3. MRV Results

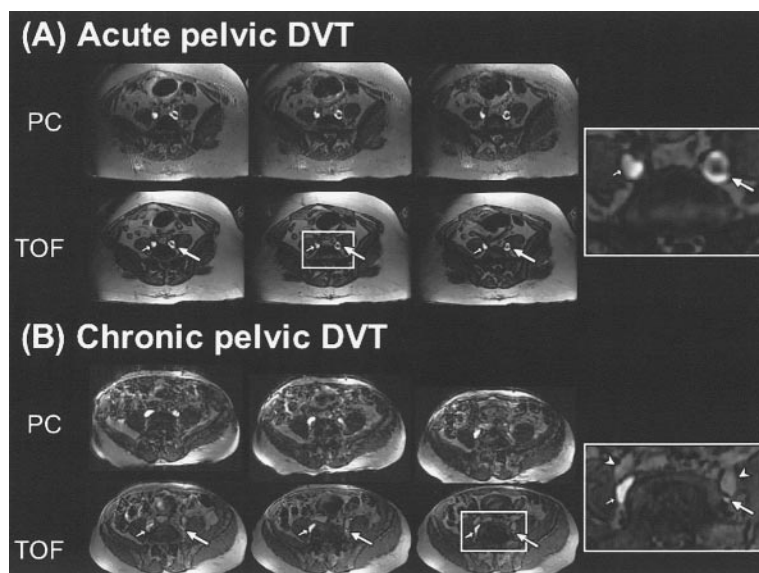
	Cause of Stroke		<i>P</i> *
	Determined	Cryptogenic	
High probability for pelvic DVT, n (%)	2/49 (4)	9/46 (20)	0.025
Acute DVT	0/47 (0)	3/40 (7)	0.093
Chronic DVT	2/49 (4)	6/43 (13)	0.140
High probability for pelvic DVT in presence of PFO or ASD, n (%)	0/9 (0)	6/28 (21)	0.302
High or intermediate probability for pelvic DVT, n (%)	4/49 (8)	12/46 (26)	0.028

*Using 2-tailed Fisher's exact test.

The 95 patients underwent pelvic MRV 48.9 ± 16.1 hours after stroke onset. Scanning did not conform to the protocol in 13 patients: The entire infrarenal inferior vena cava was not visualized in 9 patients, a superior saturation band was applied to both TOF and PC images in 3 patients, and only TOF images were acquired in 1 patient with a normal scan.

A pelvic DVT (the Figure) was present with high probability in 11 patients (Table 3). The prevalence of pelvic DVT was significantly higher ($P < 0.025$) in patients with cryptogenic stroke (9 of 46, 20%) than in patients with stroke of determined origin (2 of 49, 4%). The difference in percentages was significant whether we considered only scans with a high probability for DVT (difference, 16%; 95% confidence interval [CI], 3.2 to 28.8) or scans with intermediate or high probability for DVT (difference, 18%; 95% CI, 3.2 to 32.8). When only the 39% of study patients with PFO or atrial septal defect were examined, a pelvic DVT was present more often in patients with cryptogenic stroke, but this difference was not significant (Table 3).

In the 11 patients with high probability for pelvic DVT, MRV were acquired a mean of 41.7 hours after stroke onset. Thrombi involved external iliac vein in 6, common iliac vein in 4, and internal iliac vein in 1. Most DVT had a chronic appearance. Three of these 11 patients had received intrave-



MRV images from 2 cryptogenic stroke patients with pelvic DVT. Top row shows 3 contiguous PC MRV images; bottom row, coplanar TOF images. Long arrows indicate affected vein, which was left common iliac vein for both; short arrows, normal (right) common iliac vein. Left to right is in the direction from the heart to the foot. A, Patient with high probability for acute DVT. Left common iliac vein has a mural-based filling defect. Superior saturation band was inadvertently applied to TOF images, diminishing signal from arteries. B, Patient with high probability for chronic DVT. Left common iliac vein is narrowed. Arrowheads indicate common iliac arteries that, unlike the veins, are symmetrical.

nous tissue plasminogen activator (tPA) for acute stroke; in all 3, DVT had a chronic appearance. The 11 patients with high probability for pelvic DVT compared with the 84 other patients had a higher NIH stroke scale score (8.2 ± 6.5 versus 4.9 ± 4.5 , $P < 0.04$). Of these 11, none had a prior stroke or DVT, and no DVT risk factor was significantly different compared with patients without a pelvic DVT, although there was a trend toward a higher rate of prior miscarriage among female patients with a pelvic DVT (67% versus 12%, $P = 0.062$). During interrater reliability assessments, the second radiologist found a high probability for DVT in 4 of the 11 MRVs initially diagnosed with a high probability for pelvic DVT and found the scan to be negative in 29 of the 34 MRVs that were initially negative for DVT. With these values, $\kappa = 0.23$, representing a fair²⁵ level of interrater agreement.

Of the 9 cryptogenic stroke patients with high probability for pelvic DVT, all underwent echocardiographic evaluation, which showed PFO in 6. Of the remaining 3 patients, features of history suggested DVT in 2: 1 had an airplane flight the day before stroke and was assessed by transthoracic echocardiogram, and 1 had a history of spontaneous abortion. All 6 hypercoagulation tests were performed in 7 of 9, normal in all cases.

Of the 2 patients with stroke of determined origin and high probability for pelvic DVT, both had a large-artery stroke, had chronic appearance to pelvic DVT, received intravenous tPA acutely, and had PFO by transthoracic echocardiogram.

Discussion

A number of studies have found that PFO is present with increased frequency in patients with cryptogenic stroke.⁴ This increase suggests that, in some of these patients, a venous thrombus may be crossing to the arterial circulation and causing stroke. In the present study, MRV was used to evaluate pelvic veins early after stroke onset. Compared with patients with stroke of determined origin, patients with cryptogenic stroke had a significantly increased frequency of pelvic DVT.

The prevalence of DVT in prior studies of patients with PFO and cryptogenic stroke has varied widely, possibly because a consistent evaluation of the venous system was not performed early after stroke onset. Gautier et al²⁶ performed venography 2 days to 7 months after cryptogenic transient ischemic attack or stroke and found that 3 of 23 patients with PFO had leg DVT and 3 had common iliac vein compression. Ranoux et al²⁷ performed venography within 4 weeks of cryptogenic stroke and found that 1 of 13 patients with PFO had leg DVT. Lethen et al²⁸ performed venography an average of 8 days after transient ischemic stroke or stroke of suspected cardiac origin and found that 5 of 53 patients with PFO had iliac or calf DVT. Stollberger et al²⁹ found leg or pelvic DVT in 19 of 29 patients with PFO days to months after cryptogenic arterial embolus. The present study found pelvic DVT a mean of 2 days after stroke in 9 of 46 patients with cryptogenic stroke and in 6 of 28 patients with cryptogenic stroke and PFO.

Isolated pelvic DVT has historically been considered rare but recently has been increasingly recognized as an important

clinical entity. The infrequency with which pelvic DVT has been diagnosed in the past may be due to a number of reasons,³⁰ particularly the limited sensitivity of contrast venography, ¹²⁵I-fibrinogen scanning, and Doppler for DVT in the pelvic veins.^{11,31–33} However, autopsy studies have found that pelvic veins were the only embolic source in 19 of 86 patients (22%) with paradoxical embolism in whom a source could be found,^{9,10} and isolated pelvic DVT was found in 16% of patients with PE.⁸ Spritzer et al,¹¹ in 769 consecutive MRV studies of the entire leg and pelvis, found that 20% of DVT were isolated to the pelvic veins.

Several factors may have reduced the likelihood of diagnosing pelvic DVT in the present study. Rates of intravenous tPA (Table 2) were 10-fold greater than the US average,³⁴ which may have dissolved some DVT before MRV. Interrater reliability for MRV interpretation was not high despite efforts to refine MRV diagnostic criteria and intersite consistency of MRI manufacturer/field strength. This may have reduced the strength of the association observed between a diagnosis of pelvic DVT and particular stroke subtypes. Newer methods for evaluating pelvic DVT^{16,35–37} might show improved interrater reliability and therefore might identify a stronger relationship between pelvic DVT and cryptogenic stroke.

The present study found that patients with cryptogenic stroke have an increased prevalence of pelvic DVT compared with patients with stroke of determined origin. Most patients with cryptogenic stroke and pelvic DVT also had a PFO, a combination of results that suggests paradoxical embolism as the stroke mechanism. Strengths of the study include imaging before the time when most DVT develops after stroke and a focus on younger patients in whom the connection between PFO and cryptogenic stroke is stronger.⁴ Weaknesses of the study include the absence of a screening log, which complicates generalization of study results, and lack of data on prestroke antithrombotic medication usage, which, if different across groups (as suggested by risk factor imbalances in Table 1), might explain in part the lower DVT rate among patients with stroke of determined origin. Also, the study would have provided greater insight into the significance of pelvic DVT and might have been more precise in classifying strokes as cryptogenic if echocardiography, hypercoagulable testing, leg vein duplex, and carotid duplex had been standardized and if maximally sensitive methods³⁸ had been used to search for a PFO. Furthermore, such an approach might have lent clarity to the diagnosis of pelvic DVT in the 3 cryptogenic stroke patients who were not diagnosed with PFO.

A substantial number of patients continue to be discharged without knowledge of stroke mechanism.^{1–3} The present results suggest that paradoxical embolus from the pelvic veins may be the cause of stroke in a subset of patients classified as having cryptogenic stroke.

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